REMARKS

Applicants respectfully request reconsideration of this Application.

Previously pending claims 1576-2160 are cancelled herein. New claims 2161-3143 are added herein.

I. NEW CLAIMS

New claims 2161-3143 have been added above. Of these, ten claims (2161, 2273, 2384, 2494, 2605, 2715, 2825, 2933 and 3030) are independent. Common to all of these claims is the fixation or immobilization of a nucleic acid to a non-porous solid support.[1]

Claim 2161 is directed to a non-porous solid support comprising a single-stranded nucleic acid fixed or immobilized in hybridizable form thereto. Claims 2162-2272, which depend from claim 2161, are drawn to various embodiments as follows:

nature of non-porous siliceous substrate (claims 2162-2167);

nature of non-porous polymeric substrate (claims 2168-2174);

reactive site(s) or binding site(s) (claims 2176-2177; 2186 and 2192);

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[1] In a separate independent embodiment, claim 3030 recites "A glass or plastic solid support comprising at least one nucleic acid in hybridizable form fixed or immobilized thereto." Claims 3031-3143 depend from claim 3030.

treatment with surface treatment agent, coating solution or blocking agent (claims 2178-2185; 2187-2188; 2190-2191 and 2193-2195);

fixation/immobilization (claims 2189; and 2196-2203);

nature of nucleic acid (claims 2204-2209 and 2271-2272);

non-radioactive chemical label (claims 2210-2240);

non-radioactive signaling moiety and signal (claims 2241-2262)

photometric means (claims 2263-2266);

solid support (claim 2175 and 2267);

set comprising solid supports (claim 2268); and

non-porous system comprising solid supports (claims 2269-2270).

Claim 2273 recites "a non-porous solid support comprising reactive site(s) or binding site(s) thereon, and at least one single-stranded nucleic acid strand or sequence thereof fixed or immobilized in hybridizable form to said reactive site(s) or binding site(s)." Various dependent embodiments are provided in claims 2274-2383, which depend from claim 2273. These embodiments include:

nature of non-porous siliceous substrate (claims 2274-2279);

nature of non-porous polymeric substrate (claims 2280-2286);

reactive site(s) or binding site(s) (claims 2288; 2297; 2303);

treatment with surface treatment agent, coating solution or blocking agent (claims 2289-2296; 2298-2299; 2301-2302; and 2304-2306);

fixation/immobilization (claims 2300; and 2307-2314);

nature of nucleic acid (claims 2315-2320 and 2382-2383);

non-radioactive chemical label (claims 2321-2351);

non-radioactive signaling moiety and signal (claims 2352-2373)

photometric means (claims 2274-2377);

solid support (claim 2287 and 2378);

set comprising solid supports (claim 2379); and

non-porous system comprising solid supports (claims 2380-2381).

Claim 2384 recites "a non-porous solid support comprising reactive site(s) or binding site(s) thereon; and at least one double-stranded nucleic acid fixed or immobilized to said reactive site(s) or binding site(s), wherein at least one nucleic acid strand of said double-stranded nucleic acid comprises at least one non-radioactive chemical label which comprises a non-radioactive signaling moiety which is quantifiable or detectable." Other embodiments are provided in claims 2385-2493, which depend from claim 2384. These include:

nature of non-porous siliceous substrate (claims 2385-2390);

nature of non-porous polymeric substrate (claims 2391-2397);

reactive site(s) or binding site(s) (claims 2407; 2413);

treatment with surface treatment agent, coating solution or blocking agent (claims 2399-2406; 2408-2409; 2411-2412; and 2414-2416);

fixation/immobilization (claims 2410; and 2417-2424);

nature of nucleic acid (claims 2425-2430 and 2492-2493);

non-radioactive chemical label (claims 2431-2461);

non-radioactive signaling moiety and signal (claims 2462-2483)

photometric means (claims 2484-2487);

solid support (claim 2398 and 2488);

set comprising solid supports (claim 2489); and

non-porous system comprising solid supports (claims 2490-2491).

Claim 2494 is drawn to a system which comprises a non-porous solid support comprising reactive site(s) or binding site(s) thereon; and at least one single-stranded nucleic acid or sequence thereof fixed or immobilized in hybridizable form to said reactive site(s) or binding site(s). Claims 2495-2604, which depend from claim 2494, are directed to the following embodiments:

nature of non-porous siliceous substrate (claims 2495-2500);

nature of non-porous polymeric substrate (claims 2501-2507);

reactive site(s) or binding site(s) (claims 2509; 2524; 2518);

treatment with surface treatment agent, coating solution or blocking agent (claims 2510-2517; 2519-2520; 2522-2523; and 2525-2527);

fixation/immobilization (claims 2521 and 2528-2535);

nature of nucleic acid (claims 2536-2541 and 2603-2604);

non-radioactive chemical label (claims 2542-2572);

non-radioactive signaling moiety and signal (claims 2573-2594)

photometric means (claims 2595-2598);

solid support (claim 2508 and 2599);

set comprising solid supports (claim 2600); and

system (claims 2601-2602)

array (claim 2604).

Claim 2605 recites "a system which comprises a non-porous solid support comprising reactive site(s) or binding site(s) thereon, and at least one double-stranded nucleic acid fixed or immobilized to said reactive site(s) or binding site(s), wherein at least one nucleic acid strand of said double-stranded nucleic acid comprises at least one non-radioactive chemical label which comprises a non-radioactive signaling moiety which is quantifiable or detectable." Depending from claim 2605, claims 2606-2714 are

directed to the following embodiments:

nature of non-porous siliceous substrate (claims 2606-2611);

nature of non-porous polymeric substrate (claims 2612-2618);

reactive site(s) or binding site(s) (claims 2628; 2634 and 3634);

treatment with surface treatment agent, coating solution or blocking agent (claims 2620-2627; 2629-2630; 2632-2633; and 2635-2637);

fixation/immobilization (claims 2631 and 2638-2645);

nature of nucleic acid (claims 2646-2651 and 2713-2714);

non-radioactive chemical label (claims 2652-2682);

non-radioactive signaling moiety and signal (claims 2683-2704)

photometric means (claims 2705-2708);

solid support (claim 2619 and 2709);

set comprising solid supports (claim 2710); and

system (claims 2711-2712).

Claim 2715 is directed to an array of various single-stranded nucleic acids or sequences thereof in hybridizable form, said array comprising a non-porous solid support having reactive site(s) or binding site(s) thereon, wherein said various single-stranded nucleic acids or sequences thereof are fixed or immobilized to said reactive

site(s) or binding site(s). Dependent claims 2716-2824 provide the following embodiments:

nature of non-porous siliceous substrate (claims 2716-2721);

nature of non-porous polymeric substrate (claims 2722-2728);

reactive site(s) or binding site(s) (claims 2730; 2739 and 2745);

treatment with surface treatment agent, coating solution or blocking agent (claims 2731-2738; 2740-2741; 2743-2744; and 2746-2748);

fixation/immobilization (claims 2742 and 2749-2756);

nature of nucleic acid (claims 2757-2762);

non-radioactive chemical label (claims 2763-2793);

non-radioactive signaling moiety and signal (claims 2794-2815)

photometric means (claims 2816-2819);

solid support (claim 2729 and 2820);

set comprising arrays (claim 2821); and

system comprising arrays (claims 2822-2824).

Claim 2825 is drawn to an array of various single-stranded nucleic acids or sequences thereof in hybridizable form, said array comprising a non-porous solid support having reactive site(s) or binding site(s) thereon, wherein said various single-

stranded nucleic acids or sequences thereof are fixed or immobilized to said reactive site(s) or binding site(s). Dependent from claim 2825 are claims 2826-2932, which provide the following embodiments:

nature of non-porous siliceous substrate (claims 2826-2831);

nature of non-porous polymeric substrate (claims 2832-2838);

reactive site(s) or binding site(s) (claims 2848; and 2854);

treatment with surface treatment agent, coating solution or blocking agent (claims 2840-2847; 2849-2850; 2852-2853; and 2855-2857);

fixation/immobilization (claims 2851 and 2858-2865);

nature of nucleic acid (claims 2866-2871);

non-radioactive chemical label (claims 2872-2902);

non-radioactive signaling moiety and signal (claims 2903-2924)

photometric means (claims 2925-2928);

solid support (claim 2839 and 2929);

set comprising arrays (claim 2930); and

system comprising arrays (claims 2931-2932).

Claim 2933 recites "an array of various nucleic acid strands or sequences thereof, said array comprising a non-porous solid support having wells or depressions,

and said various nucleic acid strands or sequences fixed or immobilized in hybridizable form thereto." Claims 2934-3029 depend from claim 2933 and they provide various embodiments including the following:

nature of non-porous siliceous substrate (claims 2934-2937);

nature of non-porous polymeric substrate (claims 2938-2942);

reactive site(s) or binding site(s) (claims 2943; and 2949);

treatment with surface treatment agent, coating solution or blocking agent (claims 2944-2948; 2950; and 2952-2955);

fixation/immobilization (claims 2951 and 2956-2962);

nature of nucleic acid (claims 2963-2968);

non-radioactive chemical label (claims 2969-2999 and 3003);

non-radioactive signaling moiety and signal (claims 3004-3021)

photometric means (claims 3022-3025);

solid support (claim 3026);

set comprising arrays (claim 3027); and

non-porous system comprising arrays (claims 3028-3029).

Finally, new claim 3030 is directed to a glass or plastic solid support comprising at least one nucleic acid in hybridizable form fixed or immobilized thereto. Claims 3031-3143 depend from claim 3030 and they include the following embodiments:

nature of non-porous siliceous substrate (claims 3031-3035);

nature of non-porous polymeric substrate (claims 3036-3042);

reactive site(s) or binding site(s) (claims 3044-3045; 3054 and 3060);

treatment with surface treatment agent, coating solution or blocking agent (claims 3046-3053; 3055-3056; 3058-3059; and 3061-3063);

fixation/immobilization (claims 3057 and 3064-3071);

nature of nucleic acid (claims 3072-3078 and 3142-3143);

non-radioactive chemical label (claims 3079-3109);

non-radioactive signaling moiety and signal (claims 3110-3131)

photometric means (claims 3132-3135);

solid support (claim 3043; 3136-3138);

set comprising solid supports (claim 3139); and

non-porous system comprising solid supports (claims 3140-3141).

Entry of new claims 2161-3143 is respectfully requested. The Application supports these claims. Note, for example, that in numerous instances the Application

discusses or refers to the fixation of nucleic acids to a solid support, particularly non-porous solid supports. A list including 24 examples of such instances appears in the table below.

No.	Citation in Specification	Description
1.	Page 10, Lines 2-5	The **analyte**,...is,...**fixed** in hybridizable form **to a solid support**.
2.	Page 10, Lines 7-9	...**analytes**...directly **fixed to** a suitable **solid support**.
3.	Page 10, Lines 10-11	Alternatively, the **analyte** may be directly **fixed to** the **support**...
4.	Page 10, Lines 15-17	...the analyte is hybridized to a polynucleotide **sequence** that is **fixed to** the **solid support**.
5.	Page 10, Lines 18-20	...it is preferred that the **solid support to which** the **analyte** is **fixed** be **non-porous and transparent**, such as glass, or alternatively, plastic...
6.	Page 10, Lines 26-27	It is also highly desirable that the **analyte** be

		easily **fixed to** the **solid support**.
7.	Page 10, Lines 27-28	The capability to easily **fix** the **analyte to** a **transparent substrate**...
8.	Page 14, Lines 1-3	It may also be desirable for both the **solid support to which** the **analyte** is **fixed**...
9.	Page 14, Lines 28-29	...a **non-porous solid support to which** a **polynucleotide** is directly **fixed** in hybridizable form.
10.	Page 15, Lines 9-10	...**fixing** the **analyte to** a **non-porous solid support**...
11.	Page 15, Lines 13-15	...an **analyte** is **immobilized on a solid support**, preferably a **non-porous** translucent or transparent support.
12.	Page 15, Lines 16-17	To effect easy **fixing** of a denatured single-stranded DNA **sequence to a glass support**...
13.	Page 21, Lines 30-31	...**fixation** of single-stranded **analyte to a solid support**...
14.	Page 22, Lines 34-36	...**fixing or immobilization of DNA to non-**

		porous siliceous **solid supports**, such as glass and plastic, is also provided...
15.	Page 23, Lines 13-15	...**fixing** the polynucleotide **analyte** sequence directly **to** a **non-porous solid support**,...
16.	Page 26, Original Claim 1	**fixing** said polynucleotide **sequence to a solid support** in hybridizable form
17.	Page 26, Original Claim 5	...said solid support is **non-porous**.
18.	Page 26, Original Claim 6	...said solid support is **transparent or translucent**.
19.	Page 27, Original Claim 7	...said solid support is selected from the group consisting of **glass, plastic**, polystyrene, polyethylene, dextran and polypropylene.
20.	Page 27, Original Claim 9	...said polynucleotide **sequence** is **directly fixed to said solid support**.
21.	Page 27, Original Claim 10	...said polynucleotide **sequence** is **fixed to said solid support** in single stranded form.
22.	Page 29, Original Claim 24	**A non-porous solid support having directly fixed thereto a polynucleotide sequence in**

		hybridizable form.
23.	Page 30, Original Claim 26	...said support is a **transparent or translucent** support.
24.	Page 31, Abstract of the Disclosure	Polynucleotide sequences...are detected by a method involving **fixing of the sequences on a solid support**...

II. DECLARATION OF DR. DOLLIE M. W. KIRTIKAR

Filed herewith, and attached hereto as Exhibit A, is the Declaration of Dr. Dollie M.W. Kirtikar, a named inventor of the above-captioned application. Among other things, paragraphs 7-10 of Dr. Kirtikar's Declaration establish the following propositions:

(1) that the inventors investigated binding nucleic acids to a variety of differently shaped support materials, including flat microscope slides;

(2) that the shape of the support material was irrelevant to the surface chemistry involved; and

(3) that the inventors in fact constructed at least two arrays of different nucleic

acids, one on a flat microscope slide and the other on a flat glass fiber filter.[2]

III. NEW MATTER V. INSUFFICIENT WRITTEN DESCRIPTION

In the Office Action, the heading for the claim rejection section is "NEW MATTER IN THE CLAIMS." The body of that section refers both to new matter and to insufficient written description under 35 USC §112, 1st para. Strictly speaking, only a specification, abstract or drawings may be objected to for containing new matter. *See MPEP* §2163.06(I). Therefore, with regard to the claim rejections, Applicants refer herein to written description rather than to new matter.

IV. OBJECTION TO ABSTRACT

The Office Action points out correctly that the version of the Abstract submitted on April 10, 2002 exceeds 150 words.

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[2] These arrays included a plurality of <u>different</u> nucleic acids arranged on a single solid support. Under the plain definition of array – a plurality of (various or identical) nucleic acids arranged on a solid support – more of the inventors' experiments could be characterized as involving construction of nucleic acid arrays. See infra, discussion of meaning of array.

The Office Action also alleges that the April 10 version includes terminology that constitutes new matter. As evident below in Section VI of these Remarks, Applicants respectfully disagree that the claims are insufficiently described. For the same reasons, Applicants respectfully disagree that the April 10 Abstract contains new matter. Rather than argue over the Abstract, however, Applicants have submitted a new Abstract that broadly summarizes the invention yet lacks the allegedly offensive terminology. The submission of this new Abstract should not be interpreted as a surrender of subject matter covered by the claims.

V. REJECTION OF SYSTEM CLAIMS

The Office Action concludes that "No claim is allowed." However, the body of the Office Action only discusses the grounds for rejecting the claims that recite an array. The Office Action does not discuss the grounds for rejecting the claims that recite a system. Insofar as the recitation of an "array" without wells or depressions is the trigger for the instant rejection under §112, 1st para., the

rejection should have been applied neither to Applicants' previous system claims nor to their new system claims.[3]

Please note also that new claims 2933-3029 *are* directed to an array with wells or depressions. Therefore, the rejection should not be applied to these claims either.

[3] The new system claims are claims 2494-2714. However, claim 2604 recites that the various nucleic acids of the system comprise an array.

VI. ALLEGATION OF INSUFFICIENT DESCRIPTION OF GENERICALLY SHAPED SOLID SUPPORTS

Lost through all the years of amendments and office actions in this Application is the simple fact that, at the end of the day, all that is at issue here is a hole.[4] It was not known prior to Applicants' invention that nucleic acids could be bound to a non-porous solid support, such as glass or plastic, and yet remain hybridizable. The novelty of the invention resides in this discovery and the Patent Office has not questioned that the Application fully describes and enables this aspect. Therefore, it is difficult to understand why a feature of ZERO RELEVANCE to the novelty of the invention has generated a written description rejection.

More specifically, the Office Action rejects the array claims for lack of written description, in the context of arrays, of a generically shaped "substrate." (In the new claims, the term "substrate" has been replaced by the term "solid support." In these Remarks, the term "solid support" is generally used instead of "substrate.") The Office Action states that there is sufficient description only for arrays on solid supports that have wells or depressions. At the heart of the rejection is the mistaken notion that the originally filed Application must necessarily be limited to an array with wells or

[4] That is, a well or depression.

depressions because the *exemplified* array included wells or depressions. Therefore, according to the Patent Office, the arrays "cannot be flat and cannot permit one hybridization solution to flow over multiple immobilized hybridization probe locations."

There are several problems with the position underlying the rejection. First and foremost, it ignores the fact that the shape of the non-porous solid support has little if anything to do with the claimed invention, which relates to binding of nucleic acids in hybridizable form to the surface of a non-porous solid support, *independent of the shape of that solid support.* Second, it rejects claims over features that are not set forth in the claims. For example, despite the discussion in the Office Action of a single hybridization solution and of multiple hybridization locations, the claims refer neither to a single hybridization solution nor to multiple hybridization locations. Third, the rejection seeks to limit the application to a specific example and, in particular, to a conventional feature of that specific example. Fourth, the rejection ignores contrary declaration evidence, which *must* be considered, especially since compliance with the written description requirement is a question of fact.

These issues are discussed below in more detail in Subsections 1-4.

1. <u>The Application literally describes the solid support of the array claims</u>

There is no scientific reason whatsoever that the solid support recited in the claims must be a certain shape. The shape of the solid support has no bearing on this invention.[5] The key to the invention was getting nucleic acids to reliably bind in hybridizable form to the *surface* of a non-porous material,[6] and the chemistry of getting nucleic acids to reliably bind in hybridizable form to the surface of a non-porous material does not at all depend on the shape of the solid support.[7] In other words, the key to

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[5] The invention provides for sufficient matrix binding regardless of the shape of the solid support or its surface, be it flat (*e.g.*, plates), convex (*e.g.*, beads) or concave (*e.g.*, wells, depressions, tubes, or cuvettes). *See* Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 9, pp. 8-9. As Dr. Stavrianopoulos stated, "nowhere does the '070 specification convey that efficient hybridization-friendly fixation or immobilization of nucleic acids to a non-porous solid support depends on the shape of the surface." *Id.* *See also* Declaration of Dr. Dollie M. W. Kirtikar, para. 8 (used microscope slides, glass fibers, test tubes, microtitre plates and wells), attached as Exhibit A.

[6] *See, e.g., Id.*

[7] *See generally*, Paper 47, Declaration to Dr. Jannis G. Staviranopoulos; Paper 34, Declaration of Dr. Cheryl H. Agris; Paper 55, Declaration of Dr. James G. Wetmur. *See also* attached Declaration of Dr. Dollie M. W. Kirtikar, para. 8 ("Because the shape

this invention manifests at the molecular level, not at the macroscopic level of the shape of the solid support.

In the early 1980s, persons of skill in the art believed that nucleic acids could not be reliably bound to non-porous materials because non-porous materials have such limited capacity to bind nucleic acids consistently. Even if persons of skill at the time had thought that nucleic acids could be reliably bound to non-porous materials, they had no idea that nucleic acids could be bound in hybridizable form. Even if the persons of skill had thought that nucleic acids could be reliably bound in hybridizable form to non-porous materials, they had no idea that the binding could be specific enough to generate a reliable and accurate signal above the background noise. The Applicants' solution of these problems opened up enormous opportunities in biotechnology, particularly in the field of DNA arrays. Indeed, the elements constituting Applicants' disclosure and claimed invention are widely accepted in the art as the lynchpins of DNA microarray technology.

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of these materials is irrelevant to their surface chemistry, I used a variety of differently shaped supports to carry out these experiments, including microscope slides, glass fibers, test tubes, microtitre plates and wells.")

For instance, immediately below is an abstract of a presentation from summer 2003 on the nuts and bolts of microarray technology. Note how it mirrors Applicants' disclosure.

> **3:35 Chemistry of Printed Nucleic Acid Microarrays**
> Dr. Brian Ward, Principal Investigator Sigma-Aldrich Corporation
> Printing nucleic acids on glass microscope slides is a routine part of a **microarray** experiment. Because unmodified nucleic acids are not irreversibly immobilized on plain glass, **microscope slides need to be coated** to allow sufficient probe to be present on the slide surface for target capture and detection. **Glass is thus coated by adsorptive (e.g., with poly+lysine) or covalent (e.g., with silanes) means to enable probe immobilization**. Most commonly used amine modified surfaces (i.e., poly+lysine and aminopropyl silane) immobilize nucleic acids by a combination of coulombic attraction and surmised covalent bonding. Because binding of nucleic acids to these surfaces likely encumbers hybridization of some parts of the printed sequence, many strategies generally using amine or thiol chemistry borrowed from the bioconjugationists toolbox have been developed that attempt to tether nucleic acids to surfaces in predictive ways. The hope of these studies is to develop a tethering method that allows unencumbered probe-target hybridization. To enable an understanding of immobilization chemistry,

> glass as a substrate, silane chemistry, nucleic acid tethering, and covalent mechanisms will be reviewed.[8] [emphasis added]

The fact that Applicants' disclosure and claimed invention constitute the lynchpins of DNA microarray technology is further illustrated by the following excerpts from the book *DNA Microarrays: Gene Expression Applications -- Principles And Practice*.[9]

> The use of cDNA microarrays involves three stages that are summarized in Fig. 2.1. The **first stage** (Fig. 2.1A) involves the **preparation, arraying and attachment of DNA probes** (also known as elements) **to a non-porous substrate.... The non-porous substrate onto which the DNA probes are arrayed is typically a treated glass slide whose surface has been modified to bind DNA (traditionally coated with poly-L-lysine)**.... The second stage of expression profiling involves preparation of labeled cDNA pools (known as labelled target) from a test and reference RNA sample. Each sample is labelled using a differently fluorescently labelled nucleotide (e.g. Cy5-dCTP) for reference.... After hybridisation and washing, the third stage involves quantifying the test

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[8] From conference entitled "Macroresults for Microarrays: An Array of Possibilities," held May 12-14, 2003, World Trade Center, Boston, Mass.

[9] *DNA Microarrays: Gene Expression Applications -- Principles And Practice*, Bertrand R. Jordan (Editor), Springer-Verlag, Berlin, Heidelberg, New York, 2001.

and reference signals of each fluorophore for each element on the array....[10]

Slide chemistry consists of the way DNA is attached to the non-porous glass substrate and the subsequent inactivation of the substrate-post-arraying. When this is done efficiently, DNA elements are successfully bound to the glass surface and then inactivated to prevent labelled cDNA targets from binding to the substrate during the hybridisation, resulting in undesirable background. The **sensitivity of this technology derives from the ability to detect weak fluorescent signals at a given element on a non-porous substrate** in comparison to the very low background surrounding the elements.... **Traditionally, poly-L-lysine- or silane-coated slides have been used**.... The advantages of the poly-L-lysine chemistry are that it requires no DNA modification, it is extremely cheap and, once perfected, it provides a highly consistent performance.[11]

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[10] *Id.* at Drs. Sean Grimmond and Andy Greenfield's Chapter 2, entitled "Expression Profiling with cDNA Microarrays: A User's Perspective and Guide," submitted in the above-captioned Application with Applicants' Communication of May 8, 2003.

[11] *Id.*

The following excerpt from the book *DNA Arrays: Methods and Protocols* further illustrates the adoption in the art of Applicants' invention.[12]

> **The introduction of impermeable supports was a major departure that afforded several advantages.** As the nucleic acids form a monolayer, saturating the surface, the amount attached is consistent from one region of the array to another, and, as they are on the surface, the nucleic acids are favorably placed to take part in hybridization reactions. Interactions with the solution phase are much faster, because molecules do not have to diffuse into and out of the pores. All stages of the process benefit from this easy access. The target polynucleotides can find immediate access to the probes, accelerating hybridization, and ensuring that the multiple interactions involved in duplex formation are not perturbed by the diffusion process or any steric inhibition that may result from confinement in the pores of a membrane. Washing is also unimpeded by the need for excess labeled material to be diffused out of the pores of the membrane, which speeds up the procedure, improves reproducibility, and reduces background. All these factors are important **when the objective is to achieve reliable hybridization signals to the high level of accuracy needed to distinguish small difference in signal from different probes on the array.**[13]

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[12] *DNA Arrays: Methods and Protocols*, ed. J. Rampal (Humana 2001).

[13] *Id.* at p. 4.

To recap, prior efforts to bind nucleic acids to non-porous materials were plagued by: 1) poor binding capacity and uniformity; 2) suppression of hybridization capability; and 3) non-specific binding leading to high background (noise) signal.[14] Applicants overcame these obstacles in large part by developing surface treatments that enabled nucleic acids for the first time to be *specifically* and *uniformly* fixed to the surfaces of non-porous solid supports in quantities sufficient to exhibit favorable kinetics.[15] The uniformity of these non-porous solid supports, which stands in contrast to the nooks and crannies of porous supports in the prior art, allows for hybridization and detection of different nucleic acids under the same or similar hybridization and detection conditions.

Accordingly, the very same features disclosed in Applicants' specification were adopted in the art and therefore later described in the literature on DNA microarrays. In short, Applicants' early fixation of nucleic acids to non-porous solid supports formed the very basis for the array industry.

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[14] *See*, Paper 47, Declaration of Dr. Jannis G. Staviranopoulos, § 9, pp. 11-12.

[15] *Id.* at § 9, pp. 8-9.

A. The Application literally describes a (generic) solid support in the context of arrays

Despite the fact that the shape of the solid support in the claims is irrelevant, the Office Action essentially alleges that there is description for a solid support with wells or depressions but not for a generically shaped solid support.[18] The Office Action alleges that a generically shaped solid support encompasses a flat solid support but that the Application lacks description of a flat solid support in the context of arrays.

As discussed below, the Application literally describes a flat solid support in the context of arrays. However, the absence or presence of description of a "flat solid support" is irrelevant. The array claims do not recite that the solid support is "flat."[19] They do not recite any particular shape for the solid support. Therefore, the relevant issue is not whether there is adequate description of a "flat solid support," but whether

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[16] *See*, Paper 47, Declaration of Dr. Jannis G. Staviranopoulos, § 9, pp. 11-12.

[17] *Id.* at § 9, pp. 8-9.

[18] New claims 2933-3029 *are* directed to an array with wells or depressions.

[19] The new array claims are claims 2715-2932. New claims 2933-3029 are also directed to arrays but with wells or depressions. Based on the assertions in the Office Action, claims 2933-3029 are allowable on their face.

there is adequate description of a "solid support."[20] (For example, the solid support of claim 1 of Affymetrix's US 5,800,992, which is directed to detecting nucleic acids with arrays, is not limited to any particular shape and therefore presumably encompasses flat solid supports.[21] Yet, the '992 specification contains neither the word "flat" nor a synonym like "planar.")

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[20] *See generally Tex. Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1201 (Fed. Cir. 2002) (There is a "heavy presumption" that the terms used in claims "mean what they say and have the ordinary meaning that would be attributed to those words by persons skilled in the relevant art."); *Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.*, 34 F.3d 1048 (Fed. Cir. 1994) (A particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment.); *Resonate Inc. v. Alteon Websystems Inc.*, Nos. 02-1201, 02-1225, slip op. (Aug. 5, 2003) (Patentees are not required to claim each part of an invention with the same amount of detail.)

[21] Claim 1 of this patent, US 5,800,992, reads:

> A method for detecting nucleic acid sequences in two or more collections of nucleic acid molecules, the method comprising: (a) providing an **array** of polynucleotides bound to a **solid surface**, each said polynucleotide comprising a determinable nucleic acid; (b) contacting the **array** of

The Application clearly describes a "solid support." The Application discloses numerous solid supports of various shapes and types, including the following:

-solid supports with "surfaces,"[22]
-solid supports with "surfaces or wells,"[23]
-solid supports with "glass or polystyrene surfaces"[24]
-solid supports made of various non-porous materials,[25]
-solid supports that are transparent or translucent,[26]
-solid supports made of various "conventional" porous materials,[27]

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polynucleotides with: (i) a first collection of labelled nucleic acid comprising a sequence substantially complementary to a nucleic acid of said **array**, and (ii) at least a second collection of labelled nucleic acid comprising a sequence substantially complementary to a nucleic acid of said **array**; wherein the first and second labels are distinguishable from each other, and (c) detecting hybridization of the first and second labelled complementary nucleic acids to nucleic acids of said **arrays**. [emphasis added]

[22] Application, p. 23, 1st para.

[23] Application, p. 23, 1st para.

[24] Application, p. 20, 2nd full para., p. 23, 1st para.

[25] Application, p. 10, 1st full para., p. 22, last para.

[26] Application, p. 15, 2nd full para.

-solid supports having "arrangements" of or a "plurality" of wells, tubes or cuvettes,[28]

-"suitable" solid supports,[29]

-plates,

-plates with wells or depressions,

-plates with an array of wells or depressions,[30]

-microtiter well plates,[31]

-polystyrene plates (*i.e.*, flat-bottom Petri dishes)[32]

-tubes,

-sets of tubes,[33]

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[27] Application, p. 10, 2nd full para.

[28] Application, p. 13, last para. through p. 14, 1st full para., and original claim 17.

[29] Application, p. 10, 1st full para.

[30] Application, p. 16, 1st full para. Please note that all citations to Application page numbers and paragraphs refer to the CIP Application filed on October 31, 1992.

[31] Application, p. 23, 2nd full para.

[32] *See* Application, p. 10, 1st full para., p. 20, 2nd full para., p. 21, 1st full para., p. 22, 1st para. *See also,* Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 14, pp. 17-18; Paper 55, Declaration of Dr. James G. Wetmur, § 11, pp. 9-10, § 12, pp. 10-12.

-cuvettes,

-wells,

-"removeable wells,"[34]

-microfilter wells,[35]

-"conventional" microtiter well,[36]

-"culture media"[37]

-a transparent solid support that permits "testing of numerous samples,"[46]

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[33] Application, p. 17.

[34] Application, p. 21, 1st full para.

[35] Application, p. 22, 1st full and 2nd para.

[36] Application, p. 23, 1st full para.

[37] Application, p. 9, last para.

[38] Application, p. 10, 1st full para.

[39] Application, p. 23, 1st para.

[40] Application, p. 23, 1st para.

[41] Application, p. 20, 2nd full para., p. 23, 1st para.

[42] Application, p. 10, 1st full para., p. 22, last para.

[43] Application, p. 15, 2nd full para.

-"means for containing a fluid,"[47]

-"conventional" solid support apparatuses "employed in diagnostic laboratories,"[48]

and

-glass beads[49].

Biotechnology is sometimes considered unpredictable. In the present case, however, the shape of the non-porous solid support is a mechanical feature that raises

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[44] Application, p. 10, 2nd full para.

[45] Application, p. 13, last para. through p. 14, 1st full para., and original claim 17.

[46] Application, p. 10, 2nd full para.

[47] Application, original claims 20-23.

[48] Application, p. 13, last para.

[49] In Example 1, the Application cites a text that describes treatments for affinity binding to glass beads: Weetal, H. H. and Filbert, A. M., "Porous Glass for Affinity Chromatography Applications", Methods in Enzymology, Vol. XXXIV, Affinity Techniques Enzyme Purification: Part B, pp. 59-72, W. B. Jakoby and M. Wilchek, eds. *See also* Paper 55, Declaration of Dr. James G. Wetmur, § 11, p. 9-10, §§ 14-15, pp. 17-18.

no uncertainty or doubt as to the operation or enablement of the present invention. Moreover, the solid supports listed above clearly exceed the minimum disclosure required (if any) to describe a feature as simple and predictable as the solid support recited in the claims. Four Ph.D declarants have agreed on this point.[50]

B. Example 1 literally describes (generic) solid supports

The Office Action implies that the Application disclosure of generic solid supports is irrelevant because it does not appear in an example that explicitly refers to arrays, *i.e.*, Example 1. In other words, the Office Action implies that the Application's copious description of generic solid supports is irrelevant because this description is not recited in the context of arrays.

On the contrary, generic solid supports are disclosed in and apply throughout Example 1. Passages before, after and in Example 1 indicate that the solid support of Example 1 is meant to be generic.

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[50] *See,* Paper 47, Declaration of Dr. Jannis G. Staviranopoulos, § 9, pp. 8-9; Paper 34, Declaration of Dr. Cheryl H. Agris, § 17, pp. 9-11, § 21, pp. 15-16, § 22, p. 20; Paper 55, Declaration of Dr. James G. Wetmur, § 11, pp. 9-10, § 12, pp. 10-12, § 13, pp. 12-17, § 14, p. 17, § 15, p. 18; Declaration of Dr. Dollie M. W. Kirtikar, paras. 7, 8 and 11, attached as Exhibit A.

First, immediately before Example 1, all of the examples are expressly characterized as "illustrative of preferred embodiments."[51]

Second, the sentence in Example 1 that refers to "an array of depressions or wells" starts with the introductory words "For example."

Third, the sentence in Example 1 that refers to "an array of depressions or wells" is near the end of Example 1, but sentences that appear earlier in Example 1 refer to generic solid supports. For instance, the first sentence of Example 1 reads: "For purposes of the present invention, an analyte is immobilized on a solid support, preferably a non-porous translucent or transparent support."[52] Similarly, other sentences in Example 1 refer generically to the "glass support," the "treated glass surface," and the "treated glass."

Fourth, the first sentence in Example 2 refers to employing a "glass surface treated as described in Example 1." Yet, Example 2 uses treated glass *tubes* as the solid support. In other words, the solid support of Example 1 is generic and not limited to any particular shape.

Fifth, the specification ends with the following passage:

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[51] *See* Application, p. 15, 2nd full para.

[52] Application, p. 15, 2nd full para.

> As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations, modifications and substitutions are possible in the practice of this invention, without departing from the spirit or scope thereof. Consequently, only such limitations as appear in the appended claims should be placed upon the scope of the invention.[53]

These disclosures are not the only disclosures that the Office Action ignores. For example, the Office refers to the Office Action of October 10, 2001, which states:

> The closest array description, as filed, is given in the specification on page 16, lines 9-27 [**Example 1**].... It is additionally noted that **plastic wells** are a disclosed option as given in the bridging sentence between pages 20 and 21 [**Example 5**] of the instant specification. Polystyrene **microfilter wells** are described on page 22, lines 10-12 [**Example 6**], as a solid support.... In summary, the array embodiments, as filed, are all at least directed to solid supports with wells or depressions therein.54 [emphasis added]

The above-quoted passage from the October 2001 Office Action mentions that Example 5 recites plastic wells but it fails to mention that, in the sentences immediately before and after the sentence that includes plastic wells, Example 5 recites "polystyrene

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[53] Application, p. 25, last para.

[54] Pages 3-4 of Office Action of October 10, 2001.

plates" and "plastic surface." Indeed, Example 5 discloses more about generic plastic surfaces and polystyrene plates (flat-bottom Petri dishes) than it discloses about plastic wells.

Similarly, this passage from the October 2001 Office Action mentions that Example 6 recites microfilter wells but again it fails to mention that, in the sentences before and after the sentence that includes microfilter wells, Example 6 recites "polystyrene plates" as well as "test samples or plates," "siliceous solid supports," "surfaces" and "glass or polystyrene surfaces." Example 6 discloses as much about these solid supports as it discloses about microfilter wells. Of course, this passage from the October 2001 Office Action also ignores the other support-related disclosure set forth in Subsection 1(B) above.

Such selective picking and choosing reflects a global inconsistency and unfairness underlying the Office Action. Overall, the Office Action seeks to limit the array embodiment to the non-porous solid support of Example 1 (or, more accurately, to the non-porous solid support of the second sentence in the second paragraph of Example 1). To make its case, however, the Office Action also looks outside Example 1 to Examples 5, 6 and 7. Thus, on one hand the Office Action implies that it is proper to look outside Example 1 for evidence that Applicants are limited to Example 1. On

the other hand, however, the Office Action implies that it is improper to look outside Example 1 for evidence that Applicants are not limited to Example 1.

Indeed, this selective picking and choosing seems so egregious that Applicants wonder if there is some fundamental yet unstated assumption underlying it. If so, the Patent Office's unstated assumption may relate to the various ways that the examples refer to the non-porous solid supports. For instance, Example 5 refers to "polystyrene plates" in its second paragraph, to "wells" in its third paragraph, and to "polystyrene plates" again in its fourth paragraph.[55] Perhaps the Patent Office assumes that this alternation in terminology reflects a sloppy or inconsistent use of language and that, despite using different terms in these different paragraphs, each term refers to the same solid support. In other words, perhaps the Patent Office believes that the polystyrene plates of the second and fourth paragraphs of Example 5 in fact had wells in them and that Applicants merely neglected to point this out except in the third paragraph.

This assumption is wrong. The use of different terms for solid supports within the same individual examples was deliberate. When Applicants refer in Example 5 to

[55] Examples 6 and 7 similarly alternate between referring to polystyrene plates and wells.

polystyrene plates and then to wells and then to polystyrene plates again, it is because the initial iteration of that experiment actually employed flat-bottom Petri dishes, the second iteration actually employed wells, and the third iteration actually employed flat-bottom Petri dishes again.

C. **The Office Action improperly limits the array claims to a specific example**

Even if generically shaped solid supports were not disclosed in Example 1, it would not mean that the Application lacks description for generically shaped solid supports in the context of arrays. It is well established that an applicant may assert claims that go beyond a specific example.

> **To demand that the first to disclose shall limit his claims to** what he has found will work or to materials that meet the guidelines specified for **"preferred" materials** in a process would **not serve the constitutional purpose** of promoting progress in the useful arts. *In re Goffe*, 542 F.2d 564, 191 USPQ 429, 431 (CCPA 1976); *In re Johnson and Farnham*, 558 F.2d 1008, 194 USPQ 187, 195 (CCPA 1977). [emphasis added]
>
> **Claims need not be limited to exemplification or preferred embodiments** in order to satisfy 35 USC 112, 1st para. *Ex parte Gould*, 6 USPQ 2d 1680 (B.P.A.I. 1987). [emphasis added]
>
> A patent owner **may assert claims which go beyond the specific embodiment** shown in his application. *See Ethicon Endo-Surgery, Inc. v. United States Surgical Corp.*, 93 F.3d 1572, 1582 n.7; 40 USPQ2d 1019

(Fed. Cir. 1996) (court held that a claim – directed to a surgical stapler for which the location of a lockout mechanism was unspecified – was supported by the specification even though the specification disclosed only one location for the lockout mechanism). [emphasis added]

It is fairly **well established that a patent owner may assert claims which go beyond the specific embodiment** shown in his application. .... [For example, e]ven if the patent owner's application contained a preferred embodiment that depicted only a red barn, the patent owner would not necessarily be foreclosed from asserting a claim over a brown barn. *Reiffin v. Microsoft Corp.*, 48 USPQ2d 1274, 1276 (Fed. Cir. 1998). [emphasis added]

It is a **familiar principle** of patent law that a **claim need not be limited to a preferred embodiment**. *Lampi Corp. v. American Power products, Inc.*, 56 USPQ2d 1445, 1455 (Fed. Cir. 2000). [emphasis added]

There is **no known requirement** of law which states **that the claimed subject matter must be the subject of an example** in the specification. *Argyropoulos v. Swarup*, 56 USPQ2d 1795, 1807 (BPAI 2000). [emphasis added]

The basic principle is fleshed out in the examples presented in the PTO's Written Description Guidelines Training Materials.[56] Example 2A of the Training Materials concerns the failure to recite an *essential* limitation in the claim.

> The specification is directed to artificial hip sockets that include cup implants adapted for insertion into an acetabular, or hip, bone. The specification indicates that the shape of the cup is critical to permit the implant to effectively function as an artificial hip socket. The application describes an acetabular cup prosthesis wherein the cup is a trapezoid, a truncated cone, or of conical shape. **All of these terms describe a conical cup**. The **specification also touts the criticality of a conical cup**.... **Claim 1 is missing the element of a conical shape**. A review of the specification indicates that a cup implant having a shape which can effectively function as an artificial hip socket is critical to the operation/function of the claimed invention.... [T]he specification indicates that without the conical shape the invention will not operate as intended. Therefore, applicant was not in possession of the necessary common attributes of the elements possessed by the members of the genus. A

[56] Revised Interim Written Description Guidelines Training Materials, issued on December 21, 1999, available at www.uspto.gov/web/offices/pac/writtendesc.pdf (as of November 14, 2002).

written description rejection should be made in this situation.[57] [emphasis added]

Example 2B of the Training Materials concerns the absence in the claim of a *preferred* limitation.

> The fact situation of example 2B is similar to example 2A above except that in this example the shape of the conical cup is described as being preferred.... The specification indicates that the shape of the cup must permit the implant to effectively function as an artificial hip socket. The application describes an acetabular cup prosthesis wherein the cup is preferably a trapezoid, a truncated cone, or of conical shape. **All of these terms describe a conical cup**.... **Claim 1** in the instant application is directed to an acetabular cup prosthesis wherein the **shape of the cup is not specifically defined**...A review of the **specification indicates that a cup implant having a conical shape is preferred but has no apparent bearing to [sic] the operation/function of the claimed invention**.... Claim 1 is directed to a genus.... The disclosed species is representative of the genus because there is a known correlation between the structure and the function of claimed invention and **one of skill in the art would recognize that applicant was in possession of the necessary common attributes of the elements possessed by the members of the genus**. The invention as claimed will function in its intended manner

[57] *Id.* at 15-16.

even without the specific cup shape. **No written description rejection should be made in this situation.**[58] [emphasis added]

The present case is analogous to Example 2B and not to Example 2A. Just as the shape of the cup was irrelevant to the function of the invention of Example 2B, the shape of the solid support (whether or not part of an array) is irrelevant to the function of the present invention. The chemistry of binding a nucleic acid to a non-porous solid support is the *same* regardless of whether that nucleic acid is bound to the surface of a plate or a well, or singly or in an array.[59]

In other words, the Office Action impermissibly limits the array claims to the non-essential embodiment of a specific example. More precisely, the Office Action improperly limits the array claims to a trivial feature mentioned in the second sentence in the second paragraph of Example 1, even though four Ph.D declarants stated that the specification describes the claimed array without limiting it the non-porous solid support thereof to any particular shape.

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[58] *Id.* at 17-18.

[59] *See, e.g.*, Declaration of Dr. Dollie M. W. Kirtikar, paras. 8 and 11, attached as Exhibit A.

The importance of such declaration evidence was highlighted in *In re Alton*.[60] The applicant in *Alton* claimed a variant of IFN-γ protein in which the first three amino acid residues (two cysteines and a tyrosine) of the wild IFN-γ protein had been deleted and replaced by a single methionine. The examiner rejected the claims and explained that, although Example 5 discloses substituting a methionine for the first three residues, Example 5 further discloses substituting a lysine for the asparagine at position 81.61 In other words, the examiner asserted that the claimed modification – substituting a methionine for the first three amino acids – was never disclosed independently of another modification, substituting a lysine for the asparagine at position 81.

The applicant submitted a declaration by an expert, Dr. Wall, who declared that a person of skill in the art would have understood that the applicant possessed the claimed modification independently of the modification at position 81. The examiner dismissed the declaration, contending that it was "an opinion affidavit on the ultimate legal question at issue." The Board adopted the

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[60] *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

[61] *See Id.* at 1582.

examiner's dismissal of the Wall declaration, but the Federal Circuit reversed the Board, stating:

> [Dr. Wall] states that one of ordinary skill in the art in 1983 would have known, first, that a problem involved with isolating analogs was the capacity of the amino acid sequence to form bonds with itself through disulfide bridges, and second, that deletion of cysteines would eliminate this phenomenon. According to Dr. Wall, one of ordinary skill in the art would have understood the discussion in the specification of Example 5 to be offered as an illustration of the deletion of cysteines. Therefore, **according to Dr. Wall, one of ordinary skill in the art**, knowing that deleting the first three amino acids of the complete sequence would affect disulfide bridge formation but that the existence of lysine at position 81 would not, **would have understood the specification to describe the two modifications independently**....[62] [emphasis added]
>
> We do not read the declaration as asserting an opinion on the patentability of the claimed IFN-γ analog. Rather, the **declaration is offering factual evidence in an attempt to explain why one of ordinary skill in the art would have understood the specification to describe the modification involving the deletion of the first three**

[62] *Id.* at 1582.

amino acids independently of the modification at position 81....[63] [emphasis added]

The thrust of the **examiner's response** to the declaration is that the specification must describe the precise analog claimed....This argument, however, **does not address the point that the declaration attempts to make**....The declaration addresses why the claimed subject matter, although not identical to the analog described in the specification, was in the inventor's possession....[64] [emphasis added]

The **summary dismissal of the declaration** without an adequate explanation of why the declaration failed to overcome the *prima facie* case of insufficient description **was error**.... [The examiner] provided only conclusory statements as to why the declaration did not show that a person skilled in the art would realize that Alton had possession of the claimed subject matter in 1983.[65] [emphasis added]

D. <u>The Application literally describes a flat solid support in the context of arrays</u>

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[63] *Id.* at 1583.

[64] *Id.*

[65] *See Id.* at 1583-84.

As explained above, whether the Application discloses a flat solid support is irrelevant. In any event, even if description of a flat solid support were relevant, such description is present in the Application.

The word "plate" appears throughout the Application. In common parlance, and in most scientific uses of the term, a plate is flat or substantially flat.[66] In the field of biotechnology, a plate can, depending on the context, either be entirely flat (*e.g.*, microscope slide), flat-bottomed (*e.g.*, flat-bottom petri dish), or only generally planar due to being pitted with multiple depressions (*e.g.*, microtiter plates having wells or depressions).

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[66] *See, e.g., Webster's New World Dictionary, 3rd ed.* ("1. a smooth, flat, relatively thin piece of metal or other material"); *Stedman's Online Medical Dictionary, 27th Edition* ("1. In anatomy, a thin, relative flat, structure."); *The On-line Medical Dictionary* ("1. A flat, or nearly flat, piece of metal, the thickness of which is small in comparison with the other dimensions; a thick sheet of metal; as, a steel plate."); *Dorland's Illustrated Medical Dictionary* ("1. a flat structure or layer, such as a thin layer of bone; see also lamina, layer, etc. 2. a dental plate. 3. a flat vessel, usually a Petri dish, containing sterile solid medium for the culture of microorganisms.").

In some instances where "plate" appears in the Application, it may be fair to assume that the disclosed plate is only generally planar. In most instances, however, the most reasonable reading of the Application is that the disclosed plates are flat-bottomed or entirely flat.[67]

The fact that some of the disclosed plates are flat-bottomed is corroborated by the following three points.

First, as Dr. Stavrianopoulos and Dr. Wetmur averred, the term "polystyrene plate" in the Application refers to a flat bottom petri dish unless the term is qualified by the term "wells."[68]

Second, as Dr. Stavrianopoulos and Dr. Wetmur averred, and as their exhibits established, the term "polystyrene plate" was understood in the art to

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[67] *See also,* Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, Exhibits 15-18.

[68] Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 14, pp. 16-36; Paper 55, Declaration of Dr. James G. Wetmur, § 12, pp. 10-12.

[69] Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 14, pp. 16-18; Paper 55, Declaration of Dr. James G. Wetmur, § 11, pp. 9-10, § 12, pp. 10-12.

refer to a flat-bottom Petri dish unless qualified by the term "wells."[70] Indeed, even a "well" or a "microtiter well" can be a flat-bottomed dish.[71]

Third, the inventors actually used flat-bottom Petri dishes to develop the initial invention.[72]

The fact that some of the disclosed plates are entirely flat is corroborated by the following four points.

First, the inventors in fact used flat microscope slides to develop the initial invention.[73] Indeed, they actually constructed arrays of different nucleic acids on flat microscope slides.[74]

Second, the specification often refers to the surface of the solid supports.[75] When one wishes to indicate that a surface is not flat, one typically

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[70] *Id.*

[71] Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 14, pp. 16-18.

[72] *Id.* at § 16, pp. 36-38.

[73] *Id.* at § 16, p. 37. *See also* Declaration of Dr. Dollie M. W. Kirtikar, paras. 7-10, attached as Exhibit A.

[74] *See* Declaration of Dr. Dollie M. W. Kirtikar, paras. 7, 10, attached as Exhibit A.

describes it with an adjective such as "curved," "concave" or the like. The absence of such qualifiers strongly suggests that the disclosed surface (and therefore the disclosed solid support) is or at least can be flat.

Third, the specification refers to solid supports having "surfaces or wells."[76] The alternative term "or" further suggests that at least some of the disclosed solid supports – those with surfaces rather than wells – are flat rather than concave.[77]

Fourth, original claim 21 and the specification disclosure that corresponds to it[78] recite a "means for containing a fluid." The means for containing a fluid consists of either a well, a tube or a cuvette.[79] Neither claim 21 nor the corresponding disclosure includes a plate as a means for containing a fluid.

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[75] Application, p. 23, 1st para.

[76] Application, p. 23, 1st para.

[77] *See* Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 16, pp. 37-38.

[78] *See* Application, pp. 13-14.

[79] *See, e.g.*, Application, p. 16, 1st full para., p. 20, 2nd full para. to p. 24, 2nd full para.

Because claim 21 and the corresponding specification disclosure deliberately exclude plates from the means for containing a fluid, they strongly suggest that at least some of the disclosed plates are not shaped like containers and do not otherwise have walls or depressions suitable for containing fluids. In other words, claim 21 and the corresponding disclosure imply that at least some of the disclosed plates are entirely flat.

2. Even if the Application lacked literal description, it would still adequately describe the solid support of the array claims because the solid support and the array are conventional features

A. The solid support is a conventional feature

The Application includes copious literal description for a generically shaped solid support. Even if the Application lacked such copious literal description, it would still include adequate description because the solid support is a conventional feature and, as established in the cases and PTO Guidelines excerpted below, conventional features of an invention require little or no written description.

> That which is **common and well known** is as if it were written out in the application and delineated in the drawings. *Webster Loom Co. v. Higgins*, 105 U.S. 580, 586 (1882). [emphasis added]

An applicant **need not expressly set forth** in his specification that which would be understood by persons skilled in the art. *In re Honn and Sims*, 364 F.2d 454, 150 USPQ 652 (CCPA 1966). [emphasis added]

Under 35 U.S.C. § 112, a specification **need not teach that which is evident** to those in the art. *In re Sureau, Kremer, and Dupre*, 373 F.2d 1002, 153 USPQ 66, 70 (CCPA 1967). [emphasis added]

Matters that are **well within the knowledge of those skilled in the art** and are generally understood by such persons **need not be expressly set forth** in a specification. *Ex parte Richter*, 185 USPQ 380, 381, 382 (BPAI 1974). [emphasis added]

The disclosure of an application embraces not only what is expressly set forth in words or drawings, but what would be understood by persons skilled in the art. Those **features that are well known are as if they were written out in the patent**. Manifestly, neither the particular type of package nor the physical state and quantity of the reagents constitutes the essence of the claimed invention. These are merely incidental features and their selection are well within the routine competency of one skilled in the art. *Ex parte Wolters and Kuypers*, 214 USPQ 735, 736 (BPAI 1979). [emphasis added]

An inventor need not explain every detail since he is speaking to those skilled in the art. What is **conventional knowledge will be read into the**

disclosure. *In re Howarth*, 654 F.2d 103, 210 USPQ 689, 691 (CCPA 1981). [emphasis added]

The specification **need not describe the conventional** nor disclose what the skilled already possess. *White Consolidated Industries, Inc. v. Vega Servo-Control, Inc.*, 214 USPQ 796, 823 (Mich. 1982). [emphasis added]

When broadened claims merely omit an unnecessary or noncritical limitation disclosed in the original specification, a court will most likely conclude that the **written description requirement is satisfied**. *See, e.g., In re Peters*, 723 F.2d 891, 221 USPQ 952 (Fed. Cir. 1983). [emphasis added]

35 USC §112 does **not require a specific teaching of** that which is **already known** to one of ordinary skill in the art. *Case v. CPC International, Inc.*, 221 USPQ 196, 201 (Fed. Cir. 1984). [emphasis added]

The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification **need not disclose what is well known** in the art. *Lindemann Maschinenfabrik GMBA v. American Hoist & Derrick Company*, 221 USPQ 481, 489 (Fed. Cir. 1984). [emphasis added]

A patent applicant **need not include** in the specification that which is already known and **available to the public**. *Paperless Accounting v. Bay*

Area Rapid Transit System, 231 USPQ 649, 653 (Fed. Cir. 1986). [emphasis added]

A patent need not teach, and **preferably omits, what is well known** in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986); *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 USPQ 2d 1737, 1743 (Fed. Cir. 1987). [emphasis added]

Every nuance of the claims is **not required to be explicitly described** in the specification. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). [emphasis added]

A **description need not be provided** for features or elements that are not essential or critical to the invention. *Ethicon Endo-Surgery, Inc. v. United States Surgical Corporation*, 93 F.3d 1572 (Fed. Cir. 1996). [emphasis added]

Only critical elements of the invention must be sufficiently described. *See Gentry allery, Inc. v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998). [emphasis added]

The standard of "conventional in the art" is supported by case law holding that a patent specification "need not teach, and **preferably omits, what is well known** in the art." **Guidelines for Examination of Patent Applications** Under the 35 U.S.C. § 112, 1st Paragraph, "Written Description" Requirement, 66 *Fed. Reg.* 1099, 1103 (Jan. 5, 2001). The

> claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.... The **absence of definitions or details for well-established terms or procedures should not be the basis of a rejection for lack of written description**. *Id.* at 1105. This is equally true whether the claimed invention is directed to a product or a process.... **If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.** *Id.* at 1106. [emphasis added]

In the *Peters* case, cited above, the invention was directed to structural elements of television sets. The original claims recited that the tips of certain structural elements were tapered. The claims were later broadened to cover tapered and non-tapered tips. The claims were rejected for lack of description for non-tapered tips. The Board upheld the rejection, but the court reversed the Board:

> No prior art was distinguished from and no rejection was overcome on the basis of the tip shape. Most importantly, **one skilled in the art would readily understand that in practicing the invention it is unimportant**

> **whether the tips are tapered**, and the board erred in determining the contrary. *Peters*, *supra* at 953. [emphasis added]
>
> The broadened **claims merely omit an unnecessary limitation that had restricted one element of the invention to the exact and noncritical shape disclosed in the original patent**. In sum, nothing in the original disclosure indicates or suggests that the tapered shape of the tips was essential or critical to either the operation or patentability of the invention. *Id*. [emphasis added]

Similarly, Applicants' specification does not describe the solid support shape as essential to the array embodiment. Although the solid support is referred to throughout the Application, it is associated with a particular shape only a minority of times, and none of those particular shapes is described as important to the invention. Furthermore, the shape of the solid support remains a conventional feature regardless of whether the solid support is combined with an array. There is nothing about an array being on a solid support that would inherently convert the shape of the solid support from a conventional or known feature into a non-conventional or unknown feature. In addition, solid supports of many shapes, including flat solid supports with arrays of

various biological materials on them, were known in the art before the Application was filed.[80]

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[80] *See, e.g.*, Chapter 1 of *DNA Arrays: Methods and Protocols*, p. 2, ed. J. Rampal (Humana 2001):

> These were early forerunners of the current application of DNA microarrays to the analysis of sequence diversity and levels of gene expression. In the late 1960s, Pardue and Gall (5) and Jones and Robertson (6) discovered a way of locating the position of specific sequences in the nucleus or chromosomes by carrying out the hybridization reaction on cells fixed to microscope slides (in situ hybridization, now more familiarly known as fluorescence in situ hybridization [FISH], following the introduction of fluorescent probes). The method used to fix chromosomes and nuclei to microscope slides in a way that allowed the DNA to take part in duplex formation with the probe is now used to fix DNA spotted on to slides in one microarray method. And the multicolor fluorescent labeling techniques introduced by Ried et al. (7) and Balding and Ward (8), for the analysis of multiple probes by FISH, are now used for comparative analysis of mRNAs from different sources.... The technique of analyzing multiple hybridization targets in parallel by applying them to a filter in a defined pattern, the familiar dot blot, was introduced by Kafatos et al. (12). [Kafatos, F.C., Jones, C.W., and Efstratiadis, A. (1979) Determination of nucleic acid sequence

If the Examiner nevertheless believes that the shape of the solid support is a non-conventional feature, Applicants respectfully request that the Examiner set forth the specific reasons for this particular belief.

B. The array is also a conventional feature

The Office Action does not allege insufficient written description for "array." Indeed, the Office Action implies that the Application describes both arrays and generically shaped solid supports, provided that these two features are kept separate from each other. In other words, the Office Action alleges insufficient description only for the *combination* of an array with a generically shaped solid support. Like the solid support, however, the array is a conventional feature of the claimed invention.

The everyday meaning of array is an orderly grouping or arrangement.[81] The term "array" was construed in *Affymetrix v. Hyseq*[82] with regard to three different patents

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homologies and relative concentrations by a dot hybridization procedure. Nucleic Acids Res. 7, 1541-1552.].

See also Chapter 2 of *DNA Microarrays: Gene Expression Applications – Principles and Practice*, ed. B. Jordan (Springer-Verlag 2001) ("This principle of parallel processing was already implemented in the 1970s.").

[81] *See Relume v. Dialight*, 63 F. Supp. 2d 788, 794 (E.D. Mich. 1999); *Webster's New World College Dictionary*, 3rd ed. *See also* Chapter 1 of *DNA Microarrays: Gene*

that claim DNA arrays. For one of the patents,[83] the court held that "array is construed to mean a plurality of polymers arranged on a solid support."[84] For another of the patents,[85] the court held that "array of oligonucleotides is construed to mean a plurality

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Expression Applications – Principles and Practice, p. 3, ed. B. Jordan (Springer-Verlag 2001) ("Basically, DNA arrays consist of a series of DNA segments regularly arranged on some kind of support...").

[82] *Affymetrix v. Hyseq*, 132 F. Supp. 2d 1212 (N. Dist. Cal. 1991)

[83] Claim 7 of this patent, US 5,445,934, reads:

> An **array** of more than 1,000 different groups of oligonucleotide molecules with known sequences covalently coupled to a surface of a substrate, said groups of oligonucleotide molecules each in discrete known regions and differing from other groups of oligonucleotide molecules in monomer sequence, each of said discrete known regions being an area of less than about 0.01 cm^2 and each discrete known region comprising oligonucleotides of known sequence, said different groups occupying a total area of less than 1 cm^2. [emphasis added]

[84] *Affymetrix, supra* at 1223.

[85] Claim 1 of this patent, US 5,744,305, reads:

> An **array** of oligonucleotides, the **array** comprising [(1)] a planar nonporous solid support having at least a first surface; and [(2)] a plurality

of polymers of nucleotides ranging in length from 2 to about 100 nucleotides, arranged on a solid support."[86] For the remaining patent,[87] the court held that "array of polynucleotides is construed to mean a plurality of polymers of nucleotides of length two or greater, arranged on a solid support."[88]

As evident in the cases in which "array" has been construed, an array is such a simple feature that it can only be deemed conventional unless there are specific reasons to the contrary. Furthermore, the courts that have construed "array" expressly refused to alter its plain meaning or to qualify it with limitations from the specification.[89]

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of different oligonucleotides attached to the first surface of the non-porous solid support at a density exceeding 400 different oligonucleotides per square centimeter, [(3)] wherein each of the different oligonucleotides is attached to the surface of the non-porous solid support in a different predefined region, has a different determinable sequence, and is at least 4 nucleotides in length. [emphasis added]

[86] *Affymetrix, supra* at 1225.

[87] Claim 1 of this patent, US 5,800,992, is reproduced above in footnote 7.

[88] *Affymetrix, supra* at 1228.

[89] For example, for the '934 patent, the court expressly rejected a more specific definition proffered by one of the defendants, Incyte Pharmaceuticals.

Likewise, nothing in the Application alters the plain meaning of array or otherwise converts the array into a non-conventional feature.

If the Examiner nevertheless believes that the array is a non-conventional feature, Applicants respectfully request that the Examiner set forth the specific reasons for this particular belief.

> Incyte contends that "array" means single stranded polymers synthesized monomer by monomer on spatially addressable regions of a solid support. The Court adopts the plain, ordinary meaning of the term "array." For the reasons previously discussed, the Court rejects Incyte's attempt to limit the term to arrays which Incyte argues are enabled by the specification. Incyte has failed to identify any intrinsic evidence suggesting that Affymetrix intended "array" to have any meaning other than the plain meaning of the term. *Id.* at 1223.

Similarly, for the '305 patent the court expressly rejected a more qualified definition submitted by defendant Hyseq.

> Hyseq's proffered definition is unsupported by any portion of the '305 specification or prosecution history indicating that the patentee intended that the specific terms, "array" and "oligonucleotide" be limited in this manner. Hyseq's additional limitations thus would constitute impermissible importation of limitations from the specification to the claims. *Id.* at 1225.
>
> *See also Relume*, *supra* at 794-98.

C. Federal Circuit precedent has consistently held that a specific example does not limit a conventional feature

This is not the first time that an applicant has confronted a written description rejection after attempting to generically claim a conventional aspect of the invention set forth in an example. For example, in *Kolmes v. World Fibers Corp.*, 107 F.3d 1534 (Fed. Cir. 1997), the applicant filed an amendment claiming a yarn comprising a two-strand covering overlying a two-stranded core, the covering being wrapped at the rate of 8-12 turns per inch. The accused infringer argued that the originally filed application only disclosed the claimed wrapping rate with reference to a figure showing a one-strand core. Even though the only example using the claimed critical wrapping rate of 8-12 turns per inch was presented in the context of a single-stranded core, the court concluded that the general disclosure of a two-stranded core reasonably conveyed possession of the claimed critical wrapping rate over a two-stranded core. By analogy, even if it were true that Applicants' example of an array is in the context of a solid support having wells or depressions, the general disclosure of solid supports and the specific disclosure of plates reasonably conveys possession of arrays on flat solid supports.

The Federal Circuit encountered a similar fact pattern in *Lampi Corp. v. American Power Products Inc.*, 228 F.3d 1365 (Fed. Cir. 2000). In this case, applicants

claimed a "housing having two separable half-shells" and the accused infringer argued that the claims should be limited to *identical* half-shells. Although the specification twice referred to identical half-shells, the court concluded that this represented "only a preferred embodiment." The court noted that "It is a familiar principle of patent law that a claim need not be limited to a preferred embodiment." The court stated that "identical half-shells are not critical to the invention," noting that the drawing showing identical half shells was merely a practical example of the invention. Similarly, Applicants *never state* that wells or depressions are critical to any potential embodiment much less to the claimed embodiment. Therefore, Applicants should not be limited to wells or depressions.

In sum, it is clear from Federal Circuit precedent and the written description guidelines discussed earlier an applicant should not be limited to a preferred exemplified embodiment when the embodiment is accompanied by more general disclosure or when the embodiment represents a non-critical aspect of the invention. Once again, all we are talking about in the present case is a hole.

D. Written Description Guidelines clearly show that written description rejection is improper if feature missing from claims is conventional

Below is a decision tree from the Patent Office's Written Description Guidelines Training Materials.[90] The decision tree establishes that a written description rejection is necessarily improper when, as in the present case, the feature missing from the claims is a non-critical feature and the application contains "express, inherent or implicit support for the claim as a whole."[91]

Dr. Agris explained the tree in more detail in her Declaration.[92] With regard to broadening a claim, Dr. Agris explained that the tree poses the question "Is an element(s) missing from the claim?" If the answer is "yes," the question posed is "Is the missing element(s) described by applicant as being an essential or critical feature of the new claim as a whole?" If the applicant does not describe the feature as essential or critical, the question posed is "Is there express, inherent or implicit support for the claim as a whole?" If there is such support, the written description requirement is met.

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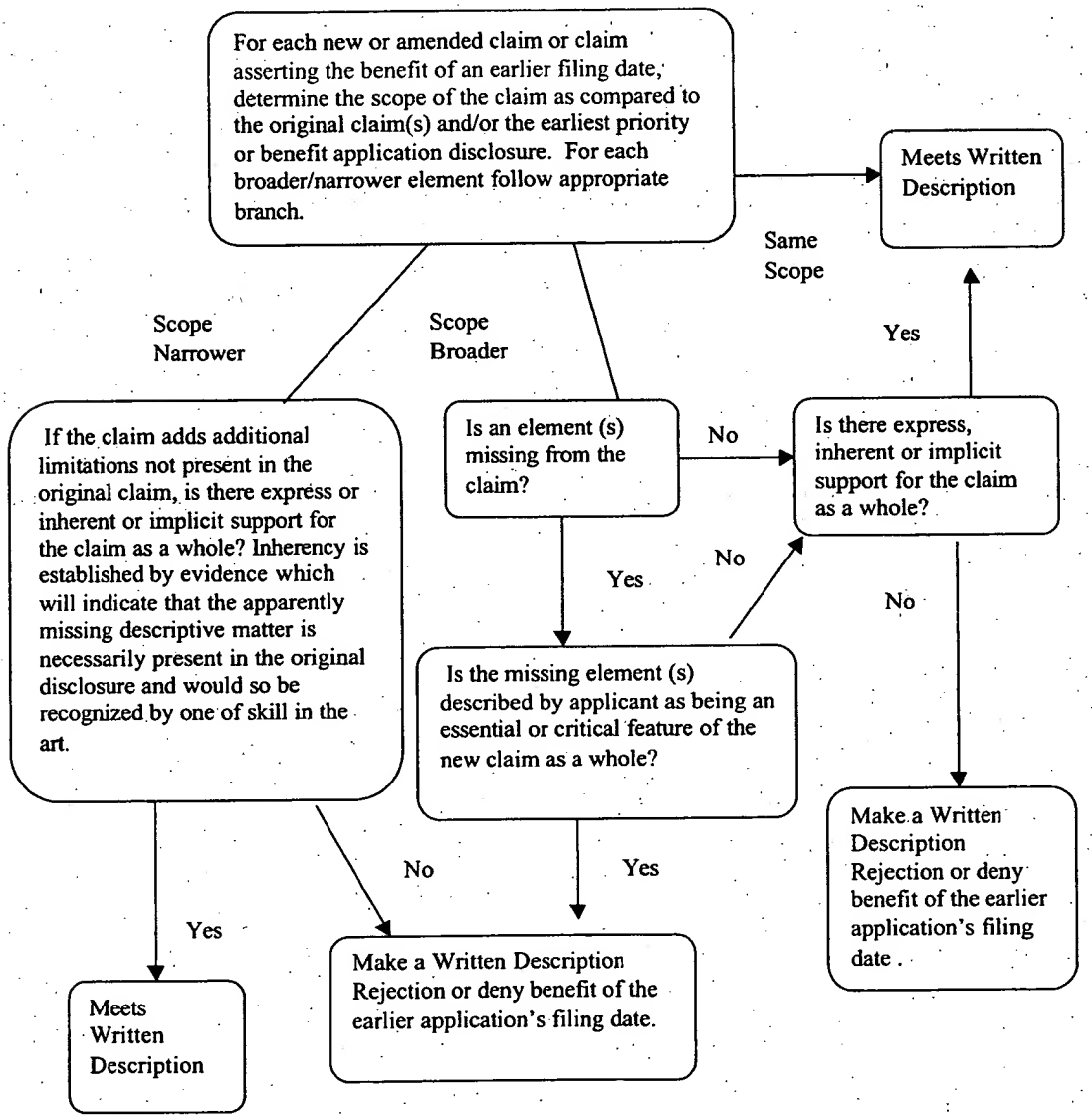
[90] Revised Interim Written Description Guidelines Training Materials, p. 6, issued on December 21, 1999, available at www.uspto.gov/web/offices/pac/writtendesc.pdf (as of November 14, 2002).

[91] *Id.*

[92] *See* Paper 34, Declaration of Dr. Cheryl H. Agris, § 25, p. 7, and Exhibit 10.

Written Description Amended or New Claims, or Claims Asserting the Benefit of an Earlier Filing Date Decision Tree



93

[93] Note that this copy of the Decision Tree differs slightly from the copy that

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appears in the Training Materials (p. 6). The copy that appears in the Training Materials includes an obvious error, namely, an extraneous arrow (with the word "No" next to it) that points from the box that asks whether the missing element is described as critical to the box in the lower right hand corner that reads "Make a Written Description Rejection." This arrow is clearly not supposed to be in the Tree. When the extraneous arrow is included, the Tree is internally inconsistent. For example, the extraneous arrow leads to a contradiction if the answer is "yes" at the box that asks whether there is express or inherent support for the claim as a whole. During a telephone conversation with Applicants' counsel on September 26, 2003, the Patent Office employee who initially drafted the Tree, Linda Therkron, agreed that the extraneous arrow was an obvious error.

3. The Office Action improperly ignores declaration evidence

Applicants previously submitted exhibits and declarations from three Ph.D declarants who unanimously and unequivocally declared that one skilled in the art would have understood that the specification discloses arrays without regard to specifically shaped solid supports. Yet, the Office Action summarily dismisses the exhibits and declarations.

> The Declaration of Dr. Stavrianopoulos, filed 6/17/02 is noted but describes disclosures, such as several **exhibits, which do not have basis as filed**. The determinative disclosure is the instant specification, abstract, and claims as filed. **Other exhibits, disclosures, etc. are moot** due to a lack of being submitted in the original filing of the instant application. Equivalently, the Declaration of Dr. James G. Wetmur cites **publications, not filed in the instant application which are therefore moot** regarding the lack of written basis as filed for the generic array claims. Dr. Wetmur also points to publications regarding immunology which are not seen as being pertinent due to being of a different subject area from the instantly claimed subject matter. Dr. Wetmur also emphasizes several disclosures supporting the well, depressions, etc. as instantly disclosed which has been previously acknowledged and **do not cure the lack of written description** of the generic arrays as now claimed. Applicants have also submitted **post-filing publications** regarding arrays, filed 12/6/02. As they are post-filing these **are moot**

> regarding the lack of written basis as filed of generic arrays as now claimed. [emphasis added]

Applicants respectfully submit that the passage above misstates the facts and the law. First, some of the most relevant of the exhibits are in fact pre-filing publications.[94] Second, Applicants did not submit the exhibits to supplement the original

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[94] For example, with regard to exhibits submitted to establish the meaning of "polystyrene plate," the following pre-filing exhibits were attached to Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos. *See* Exhibit 15, Mage et al. (1978) is "Mouse Lymphocytes With And Without Surface Immunoglobulin: Preparative Scale Separation In Polystyrene Tissue Culture Dishes Coated With Specifically Purified Anti-Immunoglobulin," *Journal of Immunological Methods* 15:47-56 (1978); Exhibit 16, Wysocki and Sato, "'Panning' for lymphocytes: A method for cell selection," *Proc. Natl. Acad. Sci.* (USA) 75:2844-2848 (June 1978); Exhibit 17, Landreth et al., "Enrichment of human marrow lymphocytes with monoclonal antibodies to murine antigens," *Proc. Natl. Acad. Sci.* (USA) 79:2370-2374 (April 1982). *See also* Exhibit 18, Haverstick et al., "Inhibition of Platelet Adhesion to Fibronectin, Fibrinogen, and von Willebrand Factor Substrates by a Synthetic Tetrapeptide Derived From the Cell-Binding Domain of Fibronectin," *Blood* 66:946-952 (1985). Haverstick et al's manuscript was submitted to

Application. Applicants submitted them to show, among other things, what the original Application would have conveyed to one skilled in the art at the time the Application was filed. The post-filing publications confirm the pre-filing publications and evidence a continuity of usage and practice (*e.g.*, with regard to "polystyrene plates") from before the filing date to after the filing date.[95]

Applicants also did not submit the declarations to supplement the original Application. The declarations likewise show what the original Application would have conveyed to one skilled in the art at the time the Application was filed. The *Alton* case, discussed above in Subsection 1(C), establishes that declarations are useful as evidence of what was in the inventors' possession. The cases and PTO Guidelines excerpted below echo *Alton* and further establish that declarations and post-filing publications are also useful as evidence of the state of the art on the filing date of an application.

Blood prior to the May 9, 1985 filing date of the second application in the family of the present Application.

[95] The Office Action also states that the submitted charts do not correlate with the specification. However, the charts were submitted with cites to locations in the specification that support each feature depicted in the charts.

Later publications are useful as **evidence of the state of the art** existing on the filing ate of an application. *In re Hogan and Banks*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977). [emphasis added]

To supplement a specification which on its face appears deficient under 35 U.S.C. § 112, **evidence must establish that the information which must be read into the specification to make it complete is known to those having ordinary skill** in the art. *In re Howarth*, 654, F.2d 103, 219 USPQ 689, 692 (CCPA 1981). [emphasis added]

A **statement by a qualified expert that the elements referred to in the application were well known to those of ordinary skill in the art is relevant**, although the expert in this case did not provide adequate support for his conclusion. *See In re Buchner*, 929 F.2d 660, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991). [emphasis added]

Beyond this evidence from the patent itself, **skilled refiners testified that the specification taught them that the inventor possessed the emission-reducing gasolines at the time of filing**.... Skilled refiners testified that they knew the composition of the claimed combinations based on this written description. Contrary to appellant refiners' arguments to this court, the record shows that refiners of ordinary skill understood and applied the '393 patent's teachings. In sum, the **record shows that the inventors possessed the claimed invention at the time of filing in the assessment of those of ordinary skill** in the petroleum refining art. *Union Oil Co. v. Atl. Richfield Co.*, 208 F.3d 989, 999, 54 USPQ2d 1227, 1234 (Fed. Cir. 2000). [emphasis added]

Upon reply by applicant, before repeating any rejection under 35 U.S.C. 112, ¶ 1, for lack of written description, review the basis for the rejection in view of the record as a whole, including amendments, arguments, and **any evidence submitted by applicant**. If the whole record now demonstrates that the written description requirement is satisfied, do not repeat the rejection in the next Office action. If the record still does not demonstrate that the written description is adequate to support the claim(s), repeat the rejection under 35 U.S.C. 112, ¶ 1, fully respond to applicant's rebuttal arguments, and properly treat any further showings submitted by applicant in the reply. When a rejection is maintained, **any affidavits relevant to the 112, ¶ 1, written description requirement, must be thoroughly analyzed and discussed in the next Office action. Guidelines for Examination of Patent Applications** Under the 35 U.S.C. § 112, 1st Paragraph, "Written Description" Requirement, 66 *Fed. Reg.* 1099, 1107 (Jan. 5, 2001). [emphasis added]

An **expert witness for Abbott testified** that in his opinion the claims of both **patents were properly fully supported**. **That testimony**, while brief, **did provide substantial evidence** supporting the jury verdict. *Abbott Laboratories v. Syntron Bioresearch Inc.*, Nos. 02-1203, 02-1257, slip. op. at 20 (Fed. Cir., July 10, 2003). [emphasis added]

In the present case, as in *Alton*, the summary dismissal of the declaration evidence is clear error.

4. <u>The allegation of insufficient description for generic solid supports in the context of arrays is arbitrary</u>

Applicants' US Patent No. 4,994,373 is based on the *same* specification as the present Application. The '373 method claims explicitly recite a "solid support" but not an "array." In the '373 method claims, the Examiner did not require that the non-porous solid support be limited to any particular shape. In light of this history, the present Office Action implies that the Examiner's position is that the disclosed solid supports are not limited to any particular shape when they are used with things other than arrays, but when the disclosed solid supports are used with arrays, they are limited to a specific shape, *i.e.*, to having wells or depressions.

There is no good reason for such splitting of hairs. The Office Action contends that the only time an "array" is mentioned in the Application it is mentioned in combination with a solid support having wells or depressions. As explained above in Subsection 1(B), Applicants disagree with this contention. In any event, this contention is not, by itself, a sustainable argument. To be sustainable, the Office Action would have to provide specific reasons why Applicants' disclosure of an array with a solid support having wells or depressions would lead a person of skill in the art to conclude that the inventors lacked possession of an array on solid supports without wells or depressions:

> The burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance, and it is **up to the PTO**

> **to give reasons why a description not in *ipsis verbis* is insufficient.** *In re Edwards, Rice, and Soulen*, 568 F.2d 1349, 196 USPQ 465, 469 (CCPA 1978). [emphasis added]
>
> If the specification contains a description of the claimed invention, albeit not in *ipsis verbis* (in the identical words), then the **examiner** or Board, in order to meet the burden of proof, **must provide reasons why one of ordinary skill in the art would not consider the description sufficient.** *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996) (citing *In re Wertheim*, 191 USPQ 90, 98 (CCPA 1976)). [emphasis added]
>
> There is a **strong presumption that an adequate written description of the claimed invention is present when the application is filed. Guidelines for Examination of Patent Applications** Under the 35 U.S.C. § 112, 1st Paragraph, "Written Description" Requirement, 66 *Fed. Reg.* 1099, 1105 (Jan. 5, 2001). The **examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description** of the invention defined by the claims. *Id.*[96] [emphasis added]

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[96] *See also* Revised Interim Written Description Guidelines Training Materials, p. 4, issued on December 21, 1999, available at www.uspto.gov/web/offices/pac/writtendesc.pdf (as of November 14, 2002).

Below are three hypothetical rejections that are analogous to the present rejection. They are analogous to the present rejection in that (a) they seem conclusory, (b) they reflect a preoccupation with a trivial feature of the invention, and (c) they declare without reasoned basis that the disclosure of a particular arrangement of the invention in a specific example fails to convey to a person skilled in the art that a similar arrangement can likewise be employed in other examples or in the general invention.

1. "Cookware" with Non-Stick Coating v. "Pots and Muffin Pans" with Non-Stick Coating. Imagine that an applicant files an application for a novel non-stick coating. The application discloses (i) the coating, (ii) examples of pots and muffin pans with the coating, and (iii) the general concept of cookware with the coating. The applicant claims, among other things, "cookware" having the coating. The examiner rejects the claim, saying:

> "Cookware" having the coating is not described. The term "cookware" encompasses flat cookware such as oven pans and cookie sheets. Only pots and muffin pans having the coating are exemplified in the application.

2. "Serving" of Spaghetti v. "Bowl" of Spaghetti. Imagine that an applicant files an application for a novel method for pressure-cooking pasta. The application discloses the method as well as examples of particular pastas prepared by the method. In a divisional of the application, the applicant claims, among other things, a "serving" of spaghetti prepared by the method. The examiner rejects the claim, saying:

> The "serving" of spaghetti prepared by the method is not described. A serving of spaghetti encompasses a flat plate of spaghetti, but in the sole example of spaghetti, the spaghetti is in a bowl, not on a flat plate. Use of flat plates is exemplified only for ravioli and macaroni prepared by the method.

3. "Corn Plant" v. "Potted Corn." Imagine that an applicant files an application for a novel insecticide. The application discloses the insecticide as well as actual test results in which the insecticide was sprayed on fields of planted wheat and soybean. In a divisional of the application, the applicant claims, among other things, a "corn plant" treated with the insecticide. The examiner rejects the claim, saying:

> "Corn plant" treated with the insecticide is not described. The term "corn plant" encompasses corn planted in a field, but in the sole example of corn, the corn is planted in pots in a greenhouse, not in a field. Being planted in a field is exemplified only for wheat and soybean.

In sum, the allegation that the Application lacks description of arrays without wells or depressions ignores the fact that possession of the invention is the relevant inquiry. As long as persons of skill in the art would reasonably find that the inventors were in possession of generically shaped solid supports in the context of arrays, the Application must be deemed to contain adequate written description for generically shaped solid supports in the context of arrays.

Applicants previously submitted declarations from three experts averring that

persons of skill in the art would find that the inventors were in possession of generically shaped solid supports in the context of arrays. The Office Action baldly dismisses the declarations.

VII. ALLEGATION OF INSUFFICIENT DESCRIPTION FOR "DIFFERENT" SEQUENCES

The Office Action alleges insufficient written description of "different" sequences on the grounds that, at least in the context of an array, the Application neither discloses different probes at different hybridization locations nor the flowing of one hybridization solution over multiple hybridization locations.

This allegation originates from essentially the same errors as the allegation of insufficient description of generically shaped solid supports. Thus, most of the points made in Section VI above apply here. Set forth below in Subsections 1 and 2 are points specific to the allegation of insufficient description of different sequences.

1. The Office Action does not focus on the claims as written

The Office Action focuses on features that are not recited in Applicants' claims. For example, the Office Action states:

The array practice, as originally filed, is limited to arrays that are comprised of **separate hybridization solutions** and/or mixtures at each different substrate location which is narrower in disclosure than the present array description in the abstract which includes any array of different hybridization probes...whereas the arrays which were disclosed, as originally filed, requires **separate hybridization mixture solutions** and therefore cannot be flat and cannot permit **one hybridization solution to flow** over multiple immobilized hybridization probe locations....It is also noted that nothing on the charts supports "different" hybridization probes at the different array locations. [emphasis added]

Similarly, the Office Action of October 10, 2001 stated:

[N]owhere in this [Cheryl H. Agris] Declaration has there been pointed to the broadening of array practice wherein **'ONE' hybridization fluid or mixture** simultaneously **washes** over all, or even a plurality, of the wells or depressions on such array surfaces. [emphasis added]

That is, whenever an array of wells etc. are described each well or depression etc. **forms** its own **hybridization reaction mixture**.... Contrary to Declarant's allegations wishing to reduce the essential nature of this array practice broadening, the application, taken as a whole or in detail focuses cleanly on **separate hybridization reaction mixtures** wherever this level of detail is described and thus is essential regarding the scope of the disclosure of this issue. [emphasis added]

None of Applicants' claims is directed to a method, recites a hybridization solution or refers to flowing or washing a single solution over multiple hybridization locations. Ultimately, therefore, the discussion of these features in the Office Action and the absence or presence of description of them are marginally relevant at best.

In this regard, the recent case of *Amgen Inc. v. Hoechst Marion Roussel Inc.*[97] is instructive. The question in *Amgen* was whether patentee's statements that its invention is "uniquely characterized" by exogenous expression of DNA meant that its claims had to be so limited. The court concluded that patentee's statements did not clearly indicate that exogenous expression was the only possible mode of the invention or that other methods were outside the stated purpose of the invention. Because of this lack of clear statement by the patentee limiting the claimed invention, the court concluded that it could not invalidate the patent for failure to describe a method of producing the claimed compositions that is not itself claimed. Nor could the patentee have described the other method, as it was not developed until 10 years later.

2. <u>The Application describes the use of different sequences</u>

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[97] *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003).

Even if description of multiple hybridization locations and the like were relevant, such description is present in the Application. The Application discloses solid supports with "surfaces" and "surfaces or wells."[98] The term "surfaces" suggests multiple hybridization locations. The alternative term "or" suggests that the hybridization locations can either be flat or concave. When a solid support includes multiple flat hybridization locations, a single hybridization solution would typically flow over all of them.[99]

Furthermore, the Application incorporates techniques that were commercially available at the time it was filed. Some of these techniques employed a single hybridization solution that flows over different probes at different hybridization locations.[100] One such technique, cited in the Background of the Invention section of the Application, was publicly known since 1975.[101]

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[98] Application, p. 23, 1st full para.

[99] *See also,* Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 16, pp. 37-38.

[100] *See* Application, p. 25, 1st full para. (incorporates ELISA techniques); p. 3, last para. (cites M. Grunstein and D.S. Hogness, Colony Hybridization: A Method for the Isolation of Cloned DNAs that Contain A Specific Gene, *Proc. Natl. Acad. Sci. USA*, 72,

In any event, even if the Application lacked explicit description of using different sequences, it would not mean that the Application lacks description of array devices on which different sequences are fixed. For one thing, the use of different sequences, like "array" and like "solid support," is a conventional feature, and a conventional feature requires little or no written description.[102] Hybridization assays were already routine in the art at the time of the invention[103]

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pp. 3961-65 (1975), and Falkow et al's US Patent No. 4,358,535 entitled "Specific DNA probes in diagnostic microbiology.")

[101] *See* Grunstein and Hogness, *supra* at 3961, 3965. This prior art method used porous nitrocellulose as the solid support. *See also* Falkow et al, *supra*.

[102] *See* case excerpts in Section V(2) above.

[103] *See* Application, p. 3, 2nd full para. *See also* J. Meinkoth and G. Wahl, Hybridization of Nucleic Acids Immobilized on Solid Supports, *Analytical Biochemistry* 138:267-284 (1984).

> I. Introduction: Two decades have elapsed since the development of methods for immobilizing DNA on nitrocellulose paper and for detecting the fixed nucleic acid with radioactive probes.... Many variations on the central theme of detection of immobilized nucleic acids have appeared in the past several years. *Id.* at 267 [citations omitted].

and, as mentioned above, it was well known at the time to use different sequences as fixed probes to test for various analytes in a single hybridization solution.

Indeed, even if the use of different sequences were deemed a non-conventional feature, and even if the Application lacked explicit description of the use of different sequences, it would not logically follow that the Application lacks description of claims to arrays that recite that different sequences are fixed thereto.

> The **test for determining compliance with the written description requirement** of 35 U.S.C. §112 is whether the disclosure of the application, as originally filed, reasonably conveys to the artisan that the **inventor had possession of the claimed subject matter, rather than the presence or absence of literal support** in the specification for the claim language. *Ex parte Harvey*, 3 USPQ2d 1626 (B.P.A.I. 1986). [emphasis added]
>
> The purpose of the written description analysis is to confirm that applicant had possession of what is claimed. **Guidelines for Examination of**

III. Detection of Nucleic Acids Immobilized on Solid Supports or in Agarose Gels: Techniques are now available for immobilizing both DNA and RNA on solid supports consisting of NC [nitrocellulose], diazotized cellulose, Ecteola cellulose, DEAE-cellulose, and nylon. *Id.* at 269 [citations omitted].

> **Patent Applications** Under the 35 U.S.C. § 112, 1st Paragraph, "Written Description" Requirement, 66 *Fed. Reg.* 1099, 1100 (Jan. 5, 2001). While the Federal Circuit has not specifically laid out a "possession" test, the Court has clearly indicated that **possession is a cornerstone of the written description inquiry**. *Id.* at 1102. The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that the applicant was in possession of the invention as now claimed. *Id.* at 1105. Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. *Id.* at 1106. [emphasis added]

Four experts declared unequivocally that persons of skill in the art would find that the inventors of the presently claimed invention were in possession of arrays with different sequences fixed thereto.[104] Yet, not only does the Office

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[104] *See*, Paper 47, Declaration to Dr. Jannis G. Staviranopoulos, §§ 18-19, pp. 39-41; Paper 55, Declaration of Dr. James G. Wetmur, § 11, pp. 9-10. Dr. Stavrianopoulos stated that "the '070 specification discloses array embodiments for one, single hybridization fluid or mixture that might contact, flow over or simultaneously permit overall hybridization." Paper 47, Declaration of Dr. Jannis G. Stavrianopoulos, § 18, p. 39. He also pointed to Examples 5 and 6 of the specification wherein "flat surfaces in the form of polystyrene plates, and glass and plastic solid supports" are

Action reject the array claims that recite different sequences, it also rejects the array claims that do *not* recite different sequences.

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disclosed and concluded "that such plates and solid supports retain or hold a single hybridization reaction mixture." *Id.* at § 18, p. 39. He also cited to several articles and product descriptions that describe the level of art at the time and that support the understanding that the "claimed array practice ...[could] be carried out in a single hybridization reaction mixture." *Id.* at § 18, pp. 39-40. Furthermore, he stated that: "the issue of whether or not array hybridization practice is carried out in a single hybridization or separate multiple hybridization solutions is not relevant to hybridization. What determines the nature of the hybridized products being formed is the identity of the nucleic acids fixed or immobilized to the non-porous substrate surfaces. Nucleic acid strands and sequences will hybridize to their complementary partner strands and sequences regardless whether a single hybridization solution or separate multiple hybridization solutions are employed in array practice." *Id.* at § 18, pp. 40-41; Declaration of Dr. Dollie M. W. Kirtikar, paras. 7, 10 and 11, attached as Exhibit A.

SUMMARY AND CONCLUSIONS

Filed herewith is a Petition for a One-Month Extension of Time with a check in the amount of $110.

New claims 2161-3143 are presented for further examination. Applicants believe that no additional claim fees are due. However, in the event that additional claim fees are due, Applicants and undersigned counsel hereby request that the Patent and Trademark Office charge the amount of any such fees and any other fee(s) due to Deposit Account No. 50-0206.

If a telephone conversation would further the prosecution of the present Application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,
HUNTON & WILLIAMS

Dated: October 31, 2003 By: _____

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Appendix A

ABSTRACT OF THE DISCLOSURE

System for nucleic acid assay and analysis, comprising non-porous solid support with nucleic acids reliably fixed or immobilized thereto in hybridizable form. The nucleic acids preferably include or interact with detectable non-radioactive labels.